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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/437,458	11/10/1999	ANTHONY GIORDANO	50093/014001	8009

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	28

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/437,458	GIORDANO ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3 and 12-37* is/are pending in the application.

4a) Of the above claim(s) *12-27 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 28, 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group 17 (claims 3, 28, 32-37; drawn towards SEQ ID NO: 17) in Paper No. 27 (filed 6/20/03) is acknowledged. Claims 12-27, 29-31 are withdrawn from consideration as being directed to nonelected inventions.

Response to Amendment

Receipt is acknowledged of a supplemental Declaration, filed 2/25/03 as Part of Paper No. 25. Receipt is also acknowledged of an amendment, filed 2/25/03 as Part of Paper No. 25, in which several claims were amended (claims 3, 28, 33) and in which new claims were added (claims 35-37). Claims 3 and 12-37 are pending in the instant application, with claims 3, 28, 32-37 drawn to SEQ ID NO: 17 under consideration as the elected invention.

Any rejection of record in the previous office action (Paper No. 23, mailed 8/23/02) not addressed herein is withdrawn. This action is FINAL.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 3, 28 and 32-37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific (i.e. specific to the claimed invention) and substantial (i.e. that does not require further experimentation to establish a specific utility) asserted utility or a well-established utility. **This rejection is maintained for reasons of record in Paper No. 23,**

mailed 8/23/02 and repeated below. The grounds for rejection are extended to new claims 35-37.

The rejected claims are directed towards an isolated fusion nucleic acid comprising a first nucleic acid (SEQ ID NO: 17) operably linked to a heterologous second nucleic acid and wherein the mRNA form of the first nucleic acids has RNA binding protein (RBP) binding activity or regulates the functionality of the mRNA form of the fusion nucleic acid. Hybrid transcripts comprising SEQ ID NO: 17 appear to be novel in the art. Therefore, there can be no well-established utility for the claimed invention.

Asserted utilities for the claimed chimeric nucleic acids include 1) screening for compounds that affect the RBP binding activity of a particular RNA/RBP binding pair interaction, and/or the mRNA functionality; 2) to identify novel RNA/RBP binding pair interactions; and 3) to modify the expression of a protein encoded by the heterologous nucleic acid portion of the chimeric nucleic acid (e.g. page 10, first paragraph of the instant specification).

SEQ ID NO: 17 is disclosed in the instant specification as being obtained from the human leptin gene (Accession No. NM_000230). The specification generally describes an experiment where a protein extract from cells known to express leptin (3T3-L1) was used to demonstrate binding by an unidentified protein or proteins (RBPs) to an undescribed RNA comprising SEQ ID NO: 17 by either filter binding assay or gel filtration. While poly r(G), heparin and "unrelated" RNAs were used as non-specific inhibitors in the binding assays, the exact composition of the competing RNAs is not disclosed by the instant specification, making it unclear how specific the observed protein binding actually was for the RNA comprising SEQ ID

NO: 17. Also, the actual binding/gel shift data is not provided by the instant specification, making it even harder to determine the specificity of the RBP/RNA interactions in this case. According to the information available at the NCBI web page for Accession No. NM_000230, the sequence represented by SEQ ID NO: 17 is present as a 3' untranslated region in the transcript encoding human leptin.

The asserted utilities are not specific in that the protein or proteins that apparently bound the RNA comprising SEQ ID NO: 17 are not identified in the instant specification. For example, using the claimed nucleic acid hybrid to identify compounds that affect a specific RNA/RBP binding pair cannot be considered to be a specific in the absence of an identified RBP specific to SEQ ID NO: 17. Moreover, the ability of the nucleic acid comprising SEQ ID NO: 17 to modify expression of a protein encoded by the fusion transcript in a specific manner (i.e. stabilize, de-stabilize, sequester, etc.) has not been demonstrated. Therefore, using the chimeric nucleic acid to modify the expression of a protein cannot be considered a specific utility. Finally, use of the claimed chimeric nucleic acid to identify novel RBP/RNA binding pairs cannot be considered specific because it is not known that the proteins that bound the RNA in the binding assay described in the specification do not also bind other RNAs (e.g. RNAs other than the unrelated RNAs used as non-specific inhibitors of binding).

The asserted utilities are not substantial in that for each of the asserted activities, it would require further experimentation in order to confirm a specific utility. For example, it would require further experimentation to determine the nature and number of different proteins responsible for binding the RNA comprising SEQ ID NO: 17 in the binding assay described in the specification. The asserted utility of using the chimeric nucleic acid to identify its own

cognate binding proteins, if any, merely constitutes further experimentation to identify a specific activity.

Claims 3, 28 and 32-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed in Paper No. 25 have been fully considered but they are not persuasive. The response essentially argues: 1) SEQ ID NO: 17 is part of the un-translated region (UTR) of a human leptin gene sequence, 2) leptin is well known in the art to be an integral component of the physiological mechanism evolved to regulate fuel stores and energy expenditure, and therefore, plays a role in obesity disorders, 3) the Revised Interim Guidelines teach that a specific utility is a "utility that is specific to the subject matter claimed", 4) the specification disclosed that RNA binding proteins (RBPs) bound specifically to SEQ ID NO: 17, 5) applicants assert the claimed nucleic acids can be used in a screening method to identify a therapeutic compound (i.e. towards regulating expression of leptin, which is of recognized value in treating obesity), 6) the Guidelines teach "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring", 7) the use of the nucleic acid sequence recited in the claims for identifying proteins that interact with this sequence satisfies the substantial utility requirement as exemplified in the guidelines, 8) no further experimentation is required in order to show that the

presently claimed sequence binds to proteins that are likely to affect leptin stability or expression, and 9) the applicants' invention is credible and the examiner has not met the burden of demonstrating that it is not credible.

The examiner does not contend that the leptin gene product is not involved in obesity disorders or that the asserted utilities for applicants' invention are incredible (e.g. in the sense of a perpetual motion machine). As was made clear in the body of the rejection, it is the nature of the protein(s) which bound the nucleic acid comprising SEQ ID NO: 17 which is not clear and is at issue. An asserted utility of identifying the proteins that bound to SEQ ID NO: 17 cannot be considered anything more than continued experimentation in order to find a specific utility for such protein (i.e. not substantial). For example, without knowing the identity of the protein(s) responsible for the gel-shift and filter-binding data cited in the specification, how can one know that the binding of the protein(s) to SEQ ID NO: 17 correlates in any way with obesity disorders? For example, if the proteins responsible for the gel shift data cited by applicants are merely housekeeping proteins, is there any utility in finding an inhibitor for such interaction? To find out, one would have to do additional experimentation in order to confirm any "real world" use for the RBPs identified as binding to SEQ ID NO: 17. Therefore, the asserted utility of identifying the RBPs that bound SEQ ID NO: 17 in the experiments cited by the disclosure cannot be considered a substantial utility.

The assertion that the claimed nucleic acids can be used to identify therapeutic compounds is not supported by the teachings of the specification. The identity and nature of the protein(s) responsible for the gel-shift and filter-binding data cited in the specification remains unknown. No regulatory activity for the UTR represented by SEQ ID NO: 17 has been

described. Therefore, it would require additional experimentation in order to confirm that the recited nucleic acids are useful in screening for compounds to treat obesity.

It is noted that the teachings of the Utility Guidelines regarding an assay to measure the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition are not applicable in this case. The invention disclosed in the specification is not one where the leptin transcript is quantified in individual using the hybrid nucleic acids of the invention, but rather encompasses the use of the hybrid nucleic acids to identify agents which affect either the functionality of the UTR of the target gene (e.g. SEQ ID NO: 17) and/or identification of agents that interfere with the RBP/hybrid nucleic acid interaction. Thus, the cited passage from the Interim Guidelines is not applicable to the invention recited in the rejected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 28, 32-35 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in Paper No. 23, mailed 8/23/02 and repeated below. The grounds for rejection are extended to new claims 35 & 37.**

The rejected claims are directed towards an isolated fusion nucleic acid comprising a first nucleic acid (SEQ ID NO: 17) operably linked to a heterologous second nucleic acid and wherein the mRNA form of the first nucleic acids has RNA binding protein (RBP) binding activity or regulates the functionality of the mRNA form of the fusion nucleic acid. Regulating functionality can comprise an alteration in pre-mRNA processing or in the stabilization, translational efficiency, localization, sequestration, editing or splicing functions. Thus, the rejected claims embrace a number of different possible effects of SEQ ID NO: 17 on a chimeric transcript comprising SEQ ID NO: 17.

SEQ ID NO: 17 is disclosed in the instant specification as being obtained from the human leptin gene (Accession No. NM_000230). The specification generally describes an experiment where a protein extract from cells known to express leptin (3T3-L1) was used to demonstrate binding by an unidentified protein or proteins (RBPs) to an undescribed RNA comprising SEQ ID NO: 17 by either filter binding assay or gel filtration. The context of SEQ ID NO: 17 in the total transcript was not described. While poly r(G), heparin and "unrelated" RNAs were used as non-specific inhibitors in the binding assays, the exact composition of the competing RNAs is not described by the instant specification, making it unclear how specific the observed protein binding actually was for the RNA comprising SEQ ID NO: 17. Also, the actual binding/gel shift data is not provided by the instant specification, making it even harder to determine the specificity of the RBP/RNA interactions in this case. There are no relevant working examples or data provided by the instant specification demonstrating the effect the presence of the sequence of SEQ ID NO: 17 on functionality of a transcript comprising SEQ ID NO: 17. No structural/functional basis is provided in the specification for one of skill in the art to envision

what are the functional effects, if any, of SEQ ID NO: 17 on a transcript comprising SEQ ID NO: 17.

According to the information available at the NCBI web page for Accession No. NM_000230, the sequence represented by SEQ ID NO: 17 is present as a 3' untranslated region in the transcript encoding human leptin. The prior art does not appear to disclose any embodiment wherein the sequence represented by SEQ ID NO: 17 has been used to modulate the functionality of any RNA, including its own. Therefore, the prior art does not offset the deficiencies of the instant specification as to the actual functional effects of SEQ ID NO: 17 on any transcript comprising the sequence.

Given that the claimed invention comprises a critical element of regulating mRNA functionality that embraces several different processes (e.g. stabilization, translational efficiency, etc.) and given the lack of a structural/functional basis in the instant specification or prior art to envision the actual effect of SEQ ID NO: 17 on a transcript comprising SEQ ID NO: 17, one of skill in the art would not be able to reliably envision the claimed invention. Therefore, one of skill in the art would reasonably conclude that applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments filed in Paper No. 25 have been fully considered but they are not persuasive. The response essentially argues: 1) a citation from the specification which asserts that applicants' have identified certain nucleic acid sequences derived from UTRs of a variety of therapeutic genes that specifically bind RNA-binding proteins (RBPs) and have discovered ways of subdividing each UTR to obtain shorter sequences that retain RNA/RBP interaction or mRNA

functionality that is equivalent to the parent sequence, 2) applicants' demonstrated the RBP binding activity of the UTR sequences in the presence of poly r(G), tRNA, heparin and unrelated RNA molecules of similar size, 3) one of skill in the art would reasonably expect a protein that specifically binds to the claimed UTR sequence to affect the functionality of the mRNA form of a fusion nucleic acid including the UTR, 4) in order to satisfy the written description requirement, one need only communicate to those skilled in the art the claimed subject matter is intended to be part of their invention, 5) the written description requirement does not require applicants to disclose every possible protein that can bind the claimed UTR sequence, 6) nor is it necessary for applicants to state how each protein that binds a UTR sequence affects the fusion nucleic acid, 7) the specification describes the general ways in which a protein can affect mRNA functionality (e.g. pre-mRNA processing, stability, translational efficiency, etc.), 8) assays for determining such functionality are standard in the art, and 9) from the start applicants have claimed the described nucleic acids as part of their invention and one of skill in the art would recognize that applicants were in possession of the claimed fusion nucleic acids.

With regard to assertions that applicants have demonstrated specific binding of SEQ ID NO: 17 in the presence of competing RNAs (e.g. poly r(G), tRNA and similarly sized RNAs), these arguments are not convincing and are off point. First, the degree of specificity for the binding observed by applicants is difficult to gauge in the absence of actual data as to the tightness of binding and/or the exact nature of the RNAs of "similar" size. Second, the grounds of the rejection are directed towards the limitations concerning RNA functionality (i.e. pre-processing of mRNA, RNA stability, etc.). Thus, even if one accepts that applicants have demonstrated some degree of specificity of binding for SEQ ID NO: 17 in the particular cell

extracts chosen for applicants' experiments, there remains no description of the functionality of SEQ ID NO: 17 with regard to the activities encompassed by the rejected claims.

With regard to arguments directed to assays for determining the functionality of given nucleotide sequence when present as part of a hybrid sequence, these arguments are better suited towards an enablement rejection. The grounds of rejection provided above are directed to a lack of sufficient description for one of skill in the art to be able to envision what functionality is conveyed by the presence of SEQ ID NO: 17 in a hybrid nucleic acid.

The assertion that one of skill in the art would reasonably expect that a protein's binding of SEQ ID NO: 17 in the context of a hybrid nucleic acid sequence would necessarily affect the functionality of the hybrid sequence is unsupported and does not address the lack of description as to exactly which, if any, functionality would be conveyed by SEQ ID NO: 17. The fact that the specification recites that there are numerous types of functionality that can be conveyed by a particular RNA sequence does not provide a basis for the skilled artisan to determine, in the absence of additional experimentation, what the functionality is for SEQ ID NO: 17.

With regard to the assertion that the skilled artisan would not doubt applicants are in possession of the claimed nucleic acids, this assertion is inaccurate as it does not address the functional limitations of the claim upon which this rejection is based. The examiner has no doubt that applicants were in possession of hybrid nucleic acids that comprise SEQ ID NO: 17. The issue is which of the functionalities recited by the rejected claims (e.g. see claim 3) is possessed by the hybrid nucleic acids comprising SEQ ID NO: 17. The fact is that the prior art and instant specification provide no basis for the skilled artisan to envision what functionality, if any, is retained by a particular nucleic acid hybrid that comprises SEQ ID NO: 17.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 32-37 are vague and indefinite in that is drawn towards non-elected embodiments (i.e. to SEQ ID NOS other than SEQ ID NO: 17). It would be remedial to amend the claim language to limit the embodiments to SEQ ID NO: 17. **This rejection is maintained for reasons of record in Paper No. 23, mailed 8/23/02.**

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

Ggl

Gerald G Leffers Jr.
GERRY LEFFERS
PRIMARY EXAMINER